PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 37/02, 9/20

A1

(11) International Publication Number: WO 93/1379

(43) International Publication Date: 22 July 1993 (22.07.9

(21) International Application Number: PCT/US93/00274

(22) International Filing Date: 8 January 1993 (08.01.93)

(30) Priority data:
820,176 13 January 1992 (13.01.92) US

(71) Applicant: PITMAN-MOORE, INC. [US/US]; P.O. Box 207, Terre Haute, IN 47808 (US).

(72) Inventors: RAMAN, Siva, N. ; 815 Walfield Court, St. Louis, MO 63141 (US). DE PRINCE, Randolph, B. ; 129 Hartland Court, Raleigh, NC 27614 (US). BLUM, Aleksander ; 2808 34th Avenue West, Seattle, WA 98199 (US).

(74) Agents: ERNST, Barbara, G. et al.; Rothwell, Figg, Ernst & Kurz, 555 13th Street, N.W., Suite 701 East, Washington, DC 20004 (US).

(81) Designated States: AU, BB, BG, BR, CA, FI, HU, JP, KI KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SI UA, European patent (AT, BE, CH, DE, DK, ES, FI GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI pater (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TI TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending th claims and to be republished in the event of the receipt c amendments.*

(54) Title: DELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES

(57) Abstract

The present invention relates to an implantable sustained release device for the sustained release of a transition metal-protein complex. The complex is combined with a substance that enhances the solubility of the complex at physiological pH. Also disclosed is a process for improving the solubility of transition metal-protein complexes at physiological pH and a process for delivering transition metal-protein complexes to a target animal. In a preferred embodiment, the transition metal is zinc and the protein is porcine somatotropin.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|---|---|---|---|---|---|
| AT | Austria | FR | France | MR | Mauritania |
| AU | Australia | GA | Gabon | MW | Malawi |
| BB | Barbados | GB | United Kingdom | NL | Netherlands |
| BE | Belgium | GN | Guinea | NO | Norway |
| BF | Burkina Faso | GR | Greece | NZ | New Zealand |
| BG | Bulgaria | HU | Hungary | PL | Poland |
| BJ | Benin | IE | Ireland | PT | Portugal |
| BR | Brazil | IT | Italy | RO | Romania |
| CA | Canada | JP | Japan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | | | SE | Sweden |
| CH | Switzerland | KR | Republic of Korea | SK | Slovak Republic |
| CI | Côte d'Ivoire | KZ | Kazakhstan | SN | Senegal |
| CM | Cameroon | LI | Liechtenstein | SU | Soviet Union |
| CS | Czechoslovakia | LK | Sri Lanka | TD | Chad |
| CZ | Czech Republic | LU | Luxembourg | TG | Togo |
| DE | Germany | MC | Monaco | UA | Ukraine |
| DK | Denmark | MG | Madagascar | US | United States of America |
| ES | Spain | ML | Mali | VN | Viet Nam |
| FI | Finland | MN | Mongolia | | |

# DELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES

## Field of Invention

This invention relates to sustained release devices capable of delivering protein complexed to transition metals to target animals over a prolonged period of time.

## Background of the Invention

Various types of sustained release devices useful for the administration of drugs, including proteins, are known. For example, U.S. Patent 4,522,625, incorporated herein by reference, relates to an oral drug dispenser comprising a wall formed of a semi-permeable material and an enteric material. The enteric material includes amino acids having an isoelectric point below a pH of 7. Amino acids also have proved useful as excipients for the controlled delivery of proteins, including somatotropins.

While these devices are useful, there have been reported problems with the amount and rate of release of some types of proteins and with the solubility of such released proteins in vivo. Such problems are particularly acute when the protein is in the form of a complex with a transition metal, such as a transition metal-protein complex which tends to be insoluble at physiological pH (7.4). Transition metals can be used to recover proteins from aqueous solutions, such as

cell culture fluids, by precipitation. The transition metal and protein form an insoluble complex which can be separated from the solution by centrifugation or precipitation. The problem, then, is getting the protein back into solution in the aqueous physiological environment.

Additionally, release of protein from some devices is in the form of an initial "burst" with declining amounts thereafter. It would be desirable to have a sustained release device having an improved and consistent rate of release of protein which remains soluble upon release. The above-described problems have been found to be particularly acute with respect to somatotropins.

Accordingly, it is an object of the present invention to provide a sustained release device which releases amounts of transition metal-protein complex at a controlled and sustained rate, wherein the protein remains soluble after release.

## Summary of the Invention

The present invention relates to a sustained release device for the release of a biologically active transition metal-protein complex and to methods of administering such a complex. The device is implantable and contains the transition metal-protein complex in combination with an excipient capable of producing a sustained release effect.

## Brief Description of the Drawings

Figure 1 is a schematic representation of an embodiment of an implant in accordance with the present invention.

Figure 2 is a schematic representation of an alternative embodiment of an implant in accordance with the present invention.

## Detailed Description of the Preferred Embodiment of Practicing the Invention

The present invention relates to a sustained release device for the release of a biologically active transition metal-protein complex after implantation of the device into a target animal. The implanted device includes the transition metal-protein complex in combination with a biologically tolerable transition metal-solubilizing substance, the combination hereafter referred to as the "matrix."

A preferred protein for use in the present invention is somatotropin. As used herein "protein", including specified proteins such as somatotropin, will include native, synthetic, or recombinant forms of proteins. Additionally, any other variants such as fragments, analogs or other polypeptides having the bioactivity of the corresponding native protein are included. Thus, any transition metal-protein complex could include any of the above variations of that protein. An especially preferred protein is porcine somatotropin.

The transition metal used in the present invention can be any suitable transition metal. Such metals are known to those of skill in this art and include, for example, Zn, Mn and Cu. The use of such metals to

recover proteins from aqueous solutions is known. See e.g. EPA 0216485A1 incorporated herein by reference. An especially preferred transition metal for use with porcine somatotropin is zinc.

For the remainder of this application, for illustrative purposes only, Zn-pST will be used as an exemplar. It is to be understood that the exemplary use of Zn-pST is not intended to limit the scope of the invention from its broader applicability to transition metal-protein complexes.

As described in more detail below, amino acids have been found to be suitable solubilizing agents for transition metals. The amino acid combined with the Zn-pST in accordance with this invention is one which enhances the solubility of the Zn-pST and, hence, its release from the device. The amino acid can be a natural or synthetic amino acid. If a natural amino acid, it is preferred that the amino acid contain a basic side chain.

The sustained release from the device is effected by providing only a portion of the device with a diffusion barrier while the remainder of the device is impermeable to the matrix, water and other excipients. A cross-section of one embodiment of the present invention is illustrated in Figure 1. An implant device made from non-toxic, innocuous materials is loaded with the Zn-pST matrix in the form of pellets 6, 8, and 10. It is to be understood that it is only this illustrated embodiment which contains 3 pellets. Other embodiments can contain any desirable number of pellets containing the Zn-pST matrix. The sides 2 and 4 of the biotolerable material are impermeable to the matrix, to water or bodily fluids, and to other excipients. As used herein, biotolerable means any material which can

be safely implanted in a biological organism. In this embodiment, a length of open-ended silicon tubing form: a satisfactory substance from which to make the device Other satisfactory substances include various polymers known to those of skill in the art, such as wax or polyethylene.

As shown in figure 1, the implant device has ends 11 and 12. Preferably, one end 11 of the devic is also impermeable to, and prevents the escape of, the matrix material. One or more glass beads inserted int one end of a silicon tube provides one effective means for achieving this purpose. Both ends can be permeabl if a faster release rate is desired, but typically onl one end 12 of the device forms a diffusion barrier. Generally, the diffusion barrier can be made from leucine or a microporous polyethylene ("MPPE") disk. Leucine barriers are preferred. Such barriers can easily be made using simple tableting procedures known to those of skill in the art.

A cross-section of a second embodiment of the present invention is illustrated in Figure 2. An implant device is loaded with pellets 6, 8, and 10 of the Zn-pST matrix. The sides and, optionally, one end 14 are impermeable to the matrix, water, bodily fluids and the other excipients. The impermeable portions in this embodiment are made from wax. Suitable waxes include animal waxes, such as beeswax, lanolin, shella wax, and Chinese insect wax, vegetable waxes such as hydrogenated soybean oil, hydrogenated cottonseed oil, carnauba, candelilla, bayberry, and sugar cane, and mineral waxes such as fossil or earth waxes (ozocerite ceresin, montan) and petroleum waxes (paraffin, microcrystalline, slack or scale wax), or combinations thereof. Pr ferably, the wax material used in the

present invention is beeswax, vegetable wax, carnauba wax, or combinations thereof.

At least one end 12 of the device forms a diffusion barrier, as described above.

The Zn-pST used in the invention can be any biologically active form of Zn-pST. As used herein, Zn-pST will include zinc complexes of native, synthetic, recombinant or other forms of porcine somatotropin. Additionally, complexes of any variants, fragments, analogs or other polypeptides having the bioactivity of native porcine somatotropins are encompassed by the term Zn-pST. Thus, for example, Δ7-rpST, a well-known recombinant variant of pST lacking seven amino acids at the N-terminus, disclosed and claimed in published European Patent Application 104,920, owned by Biogen, would be included herein.

The Zn-pST desirably is admixed with an amino acid excipient. As used herein, the term "amino acid" will include both natural and synthetic amino acids. Zn-pST has poor solubility in aqueous solutions, such as body fluids, at physiological pH (7.4). Thus, one required characteristic of the amino acid is its ability to solubilize the Zn-pST at physiological pH, i.e., amino acids producing a Zn-pST solubilizing effect are required. While not wishing to be bound by theory, it is thought that amino acids which chelate the zinc ion are particularly suitable for use in the present invention. Zn-pST is known to be soluble in alkaline aqueous solutions. Accordingly, natural amino acids having a basic side chain are preferred. Especially preferred is the amino acid arginine. The arginine can be used as a free base or in the form of arginine hydrochloride (AHCl). AHCl is particularly ffective in solubilizing recombinant Zn-pST with little or no

aggregation. It is to be understood that, armed with the teaching of the present specification, those of skill in the art could readily determine the best excipient-transition metal-protein matrices for any given protein.

In an alternative, especially preferred embodiment, a synthetic amino acid such as ethylenediaminetetraacetic acid (EDTA) can be admixed with the Zn-pST. Preferably, a trisodium salt of the EDTA is used. Reference to Table 1 illustrates that much less EDTA, as compared with natural basic amino acids, is required to solubilize the Zn-pST. It is to be understood that other synthetic amino acids can be used in the present invention, providing such amino acids solubilize Zn-pST at physiological pH.

Additionally, sucrose has been used as a stabilizer for pST, as disclosed in U.S. Patent 4,816,568, incorporated herein by reference. Advantageously, sucrose can be included in the matrix of the present invention.

When a natural amino acid is to be used, it has been found that an excess of either the amino acid or sucrose is desirable. Preferred ratios of Zn-pST to amino acid to sucrose are from about 1:3:1 to about 1:1:3, respectively, with 1:3:1 being especially preferred. When EDTA is to be used, larger amounts of Zn-pST can be included in the device. Ratios of Zn-pST to EDTA can range from about 2:1 to about 10:1, respectively. The sucrose in the embodiment utilizing EDTA preferably varies from about 6 parts to about 30 parts by weight.

Generally, the materials to be used in the matrix are sieved to a particl size of l ss than about 250 microns prior to being mixed together. Mixing can be

physical mixing with the dry ingredients in the desired ratio placed into a sterile vial and agitated. Methods of agitation are known to those of skill in the art and include, for example, the use of vortex shakers. A suitable agitation time typically is from about 5 to about 10 minutes. After about 3 minutes, if desired, 1% magnesium stearate, which functions as a tablet lubricant, can be added to the formulation.

A second desirable method of preparation involves colyophilization. In this method, the desired amount of Zn-pST is added to an aqueous solution of the desired amounts of amino acid and sucrose. The resulting solution is sonicated for a few minutes, typically for about 5 to 10 minutes. After filtering through a 0.22 micron filter the solution is lyophilized.

The resulting mixed powders from either mixing procedure preferably are pelleted. Suitable methods of pelleting are known to those of skill in the art and include the use of a Stoke's machine or a single punch press. The weight and size of the pellets can be controlled with such techniques. It has been found that pellets having diameters of from about 3.0 to 4.0 mm give preferred release characteristics. Especially preferred are pellets having about 4 mm diameters. The length of the pellet can vary but typically is about 7 mm.

As is known to those of skill in the art, it is important to sterilize all materials to be used in implants. Suitable methods of sterilization are known and do not comprise a portion of this invention.

A desired number of the resulting pellets are inserted into a sustained release device suitable for implantation into a target animal. This number will be

governed in part by the amount and duration of the desired dosage. Generally, the sustained release device will be only slightly larger than the number of pellets it is to contain. Any bio-tolerable implantable device can be used. However, for convenience, as noted above, silicone tubing is a preferred material. Especially preferred is silicon tubing having an inner diameter of about 4 mm. An implant device capable of sustained release of bioactive somatotropin for several days is preferred.

This invention also includes methods of administering Zn-pST to target animals. An implant device containing a desired amount of Zn-pST, as previously described, is implanted into a target animal. Techniques of implantation are known to persons of skill in this art, and any such implantation technique is suitable for use in the present invention. The matrix is solubilized in the target animal's body fluids and the bioactive somatotropin Zn-pST is released from the implant into the animal. The rate of release is controlled via the diffusion barrier. The somatotropin desirably is released from the device at a sustained rate over the course of several days, preferably at least about 14 days.

The present invention also relates to a process for improving the release characteristics of Zn-pST from implantable sustained release devices. Zn-pST is admixed with a substance capable of solubilizing Zn-pST at physiological pH and a desired amount of the mixture is loaded into a sustained release device. Suitable substances include natural amino acids having basic side chains and their salts, such as arginine, histidine and AHCl. Preferably, the natural amino acid is AHCl and the Zn-pST is a recombinant pST.

Alternatively, Zn-pST can be admixed with a synthetic amino acid such as EDTA.

The invention having been generally described, the following specific examples are provided for illustrative purposes and are not to be construed as limiting the invention in any manner.

Example 1: Preparation of Implant

In separate blendings, the amounts of ingredients shown in Table 1 were mixed together. Unless otherwise indicated, the reagents were obtained from commercially available sources. Zn-pST was prepared according to European Patent Application 0277043, filed January 30, 1987, which has been incorporated herein by reference.

Histidine and monosodium glutamate were sterilized by filtration through 0.2 micron Gelman Acrodiscs® and lyophilized from 3.3 and 10% w/v aqueous solutions respectively. Arginine and AHCl were not sterilized. Alanine and sucrose were autoclaved for 15 minutes and vacuum dried (76 mm) for 36 hours at 40°C. The arginine had been hydrated to a moisture content of 17%. Each ingredient was passed through a 60-mesh sieve prior to mixing. The amounts of each ingredient were directly weighed into tared, sterile vials. The pST was added first, then the amino acid and, lastly, the sucrose.

TABLE 1. Compositions of the Formulations Evaluated

| Set No. | Code | Matrix and Composition (mg) |
|---|---|---|
| 1 | ARG | ZnpST/Arginine/Sucrose 360/1080/360 |
| 2 | HCL | ZnpST/Arginine hydrochloride/Sucrose 360/1080/360 |
| 3 | ALA | ZnpST/Alanine/Sucrose 360/1080/360 |
| 4 | HIS | ZnpST/Histidine/Sucrose 360/1080/360 |
| 5 | MSG | ZnpST/L-Glutamic Acid, monosodium salt/Sucrose 360/1080/360 |
| 6 | SUHC-A | ZnpST/Sucrose 383/1532 |
| 7 | EDTA | ZnpST/EDTA/Salts/Sucrose 400/50/50/1300 |

The vials were sealed and agitated on a Vortex-Genie mixer at a setting of 10 while rotating by hand. After three minutes, 1% magnesium stearate which had been autoclaved and vacuum dried was added and the agitation continued for an additional two minutes. The resulting powder was sieved to less than 250 micron particle size and pelleted using a single punch press (Key International, Inc.) fitted with flat punches to give tablets weighing 101 mg, measuring 4.0 mm in diameter and 7 mm in length. Prior to pelleting, all contact surfaces were sterilized by wiping with 70% EtOH, flaming and exposing to UV radiation for 15 minutes. The tooling was lubricated with sterile

magnesium stearate after each compression. Three 101 mg pellets were inserted into a pre-cut sterilized piece of silicon tubing. One end of the tubing was sealed with two 4 mm solid glass beads which had been sterilized by applying dry heat at 160°C for six hours. The other end of the tubing was fitted with a 25 mg disk (4 mm diameter) made from L-leucine. Each implant contained 60 mg of pST.

Example 2: In Vitro Release Studies.

The implants from Example 1 were placed in a 20x125 mm sterile culture tube containing 8 ml of 10 mM PBS (pH 7.4). Gentamicin sulfate (100 ppm) was included to prevent bacterial contamination. The tubes were continuously shaken in a Gyrotory shaker bath (New Brunswick Scientific Co., Edison, NJ, model G76) at a speed setting of 5. The solutions were changed daily and UV spectroscopy utilized to analyze the protein concentration. A Perkin-Elmer Lambda-7 spectrophotometer was used to measure the absorbance at 276 nm. A random scattering correction was applied by measuring the absorbance at 320 nm and subtracting this value from that at 276 mm. An extinction coefficient of 0.73$mg^{-1}$ ml $cm^{-1}$ was used for the Zn-pST solutions.

The amount of ST released over 14 days increased in the order MSG<SUC<His<Ala<Arg<AHCl or EDTA. Thus, AHCl or EDTA released the greatest amount of ST. The release rate declined in all cases as the study progressed. The release data for each set is listed in Table 2. Arg, EDTA and AHCl, which released the most pST, were further tested with gel permeation chromatography, "GPC". GPC is a well-known technique and does not compris a part of the present invention. The GPC tests showed that AHCl released only monomeric

pST while the Arg matrix resulted in significant dimer formation. GPC data are set forth in Table 3.

TABLE 2. Release data for sets 1-6

| Cum Time | Set 1 | | | | Set 2 | | | | Set 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mg Rel/Day | | Cum % Rel | | Mg Rel/Day | | Cum % Rel | | Mg Rel/Day | | Cum % Rel | |
| (Days) | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| 0.4 | 25.8 | 6.9 | 15.1 | 4.0 | 11.4 | 2.6 | 6.7 | 1.5 | 8.2 | 0.4 | 4.8 | 0.3 |
| 1.0 | 8.0 | 1.1 | 23.7 | 3.2 | 8.3 | 0.6 | 15.6 | 1.2 | 5.2 | 0.4 | 10.4 | 0.4 |
| 2.0 | 4.1 | 1.3 | 30.5 | 2.0 | 5.6 | 0.4 | 25.0 | 0.9 | 3.2 | 0.1 | 15.7 | 0.5 |
| 3.0 | 2.9 | 1.2 | 35.4 | 3.2 | 4.2 | 0.2 | 32.0 | 0.6 | 2.2 | 0.1 | 19.3 | 0.7 |
| 4.0 | 1.9 | 0.4 | 38.6 | 3.0 | 3.6 | 0.1 | 38.0 | 0.6 | 1.7 | 0.2 | 22.1 | 0.7 |
| 5.0 | 1.7 | 0.4 | 41.5 | 3.6 | 3.3 | 0.1 | 43.6 | 0.7 | 1.9 | 0.1 | 25.2 | 0.7 |
| 6.0 | 1.9 | 0.4 | 44.6 | 3.1 | 3.2 | 0.2 | 48.9 | 0.7 | 1.4 | 0.1 | 27.6 | 0.6 |
| 7.0 | 1.7 | 0.1 | 47.4 | 2.9 | 2.0 | 0.2 | 52.1 | 0.7 | 1.1 | 0.1 | 29.5 | 0.7 |
| 8.0 | 1.1 | 0.6 | 49.3 | 3.1 | 1.5 | 0.1 | 54.7 | 0.7 | 1.2 | 0.1 | 31.6 | 0.7 |
| 9.0 | 0.7 | 0.2 | 50.5 | 3.1 | 1.3 | 0.0 | 56.7 | 0.7 | 1.2 | 0.1 | 33.5 | 0.8 |
| 10.0 | 0.6 | 0.1 | 51.5 | 3.2 | 1.2 | 0.0 | 58.7 | 0.7 | 1.0 | 0.1 | 35.2 | 0.8 |
| 11.0 | 0.7 | 0.3 | 52.7 | 3.4 | 1.0 | 0.0 | 60.3 | 0.7 | 0.8 | 0.1 | 36.5 | 0.8 |
| 12.0 | 0.4 | 0.1 | 53.4 | 3.4 | 0.9 | 0.1 | 61.8 | 0.7 | 0.6 | 0.0 | 37.5 | 0.8 |
| 13.0 | 0.4 | 0.1 | 54.0 | 3.5 | 0.6 | 0.1 | 62.8 | 0.7 | 0.5 | 0.0 | 38.4 | 0.8 |
| 14.0 | 0.3 | 0.1 | 54.5 | 3.5 | 0.5 | 0.1 | 63.6 | 0.8 | 0.5 | 0.0 | 39.1 | 0.8 |

TABLE 2 (continued)

| Cum Time | Set 4 | | | | Set 5 | | | | Set 6 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mg Rel/Day | | Cum % Rel | | Mg Rel/Day | | Cum % Rel | | Mg Rel/Day | | Cum % Rel | |
| (Days) | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| 0.4 | 4.8 | 1.2 | 2.8 | 0.7 | 7.1 | 0.4 | 4.1 | 0.3 | 7.1 | 0.4 | 4.1 | 0.3 |
| 1.0 | 2.1 | 0.1 | 5.1 | 0.7 | 3.8 | 0.6 | 8.3 | 0.9 | 3.8 | 0.6 | 8.3 | 0.9 |
| 2.0 | 1.6 | 0.1 | 7.7 | 0.6 | 2.8 | 0.3 | 12.9 | 1.3 | 2.8 | 0.3 | 12.9 | 1.3 |
| 3.0 | 0.9 | 0.1 | 9.1 | 0.6 | 2.0 | 0.2 | 16.3 | 1.6 | 2.0 | 0.2 | 16.3 | 1.6 |
| 4.0 | 0.3 | 0.1 | 9.7 | 0.7 | 1.3 | 0.0 | 18.5 | 1.6 | 1.3 | 0.0 | 18.5 | 1.6 |
| 5.0 | 0.4 | 0.1 | 10.2 | 0.6 | 1.2 | 0.1 | 20.5 | 1.7 | 1.2 | 0.1 | 20.5 | 1.7 |
| 6.0 | 0.2 | 0.0 | 10.6 | 0.7 | 0.8 | 0.0 | 21.8 | 1.7 | 0.8 | 0.0 | 21.8 | 1.7 |
| 7.0 | 0.1 | 0.0 | 10.8 | 0.7 | 0.6 | 0.0 | 22.9 | 1.8 | 0.6 | 0.0 | 22.9 | 1.8 |
| 8.0 | 0.1 | 0.0 | 11.0 | 0.7 | 0.6 | 0.0 | 23.9 | 1.9 | 0.6 | 0.0 | 23.9 | 1.0 |
| 9.0 | 0.1 | 0.0 | 11.2 | 0.7 | 0.5 | 0.1 | 24.7 | 2.0 | 0.5 | 0.1 | 24.7 | 2.0 |
| 10.0 | 0.1 | 0.0 | 11.4 | 0.7 | 0.5 | 0.1 | 25.5 | 2.1 | 0.5 | 0.1 | 25.5 | 2.1 |
| 11.0 | 0.1 | 0.0 | 11.5 | 0.7 | 0.4 | 0.0 | 26.2 | 2.2 | 0.4 | 0.0 | 26.2 | 2.2 |
| 12.0 | 0.1 | 0.0 | 11.5 | 0.7 | 0.3 | 0.0 | 26.7 | 2.2 | 0.3 | 0.0 | 26.7 | 2.2 |
| 13.0 | 0.0 | 0.0 | 11.7 | 0.8 | 0.2 | 0.0 | 27.2 | 2.3 | 0.3 | 0.0 | 27.2 | 2.3 |
| 14.0 | 0.0 | 0.0 | 11.7 | 0.8 | 0.3 | 0.1 | 27.6 | 2.5 | 0.3 | 0.1 | 27.6 | 2.5 |

TABLE 2. (continued) Release data for set 7

| Cum Time Days | Mg Rel/Day Mean | Mg Rel/Day SD | Cum % Rel Mean | Cum % Rel SD |
|---|---|---|---|---|
| 0.4 | 23.2 | 4.1 | 9.8 | 1.7 |
| 1.0 | 11.6 | 1.1 | 18.8 | 2.3 |
| 2.0 | 7.8 | 0.9 | 28.1 | 3.2 |
| 3.0 | 5.9 | 0.4 | 35.2 | 3.6 |
| 4.0 | 4.5 | 0.3 | 46.0 | 4.1 |
| 5.0 | 4.4 | 0.5 | 46.0 | 4.1 |
| 6.0 | 3.6 | 0.3 | 50.3 | 4.2 |
| 7.0 | 3.2 | 0.2 | 54.1 | 4.0 |
| 8.0 | 3.1 | 0.3 | 58.0 | 4.3 |
| 9.0 | 2.2 | 0.3 | 60.6 | 4.6 |
| 10.0 | 1.8 | 0.3 | 62.7 | 4.9 |
| 11.0 | 1.5 | 0.2 | 64.5 | 5.2 |
| 12.0 | 1.3 | 0.2 | 66.1 | 5.5 |
| 13.0 | 1.1 | 0.2 | 67.4 | 5.7 |
| 14.0 | 0.9 | 0.2 | 68.5 | 5.8 |

TABLE 3. GPC data for ST solutions recovered on Days 1 and 6

| Set # | Area % of monomer : dimer : aggregates* Day 1 | Day 6 |
|---|---|---|
| 1 | 67:33:0 | 54:45:0 |
| 2 | 100:0:0 | 100:0:0 |
| 3 | 100:0:0 | 100:0:0 |
| 4 | 100:0:0 | 100:0:0 |
| 5 | 100:0:0 | 100:0:0 |
| 6 | 100:0:0 | 100:0:0 |
| 7 | 100:0:0 | 100:0:0 |

Notes: * Mean values from two samples

WHAT IS CLAIMED IS:

1. An implantable sustained release device for releasing a biologically active protein which comprises a matrix comprising a mixture of a complex of said biologically active protein and a transition metal and a substance which solubilizes said complex at physiological pH.

2. The device of claim 1 wherein said protein comprises somatotropin.

3. The device of claim 2 wherein said transition metal comprises zinc.

4. The device of claim 3 wherein said somatotropin comprises porcine somatotropin.

5. The device of claim 1, wherein said matrix further comprises sucrose.

6. The device of claim 5, wherein said substance comprises a basic side group-containing natural amino acid, a synthetic amino acid or a salt thereof.

7. The device of claim 6, wherein said natural amino acid comprises arginine, histidine or arginine-HCl.

8. The device of claim 7, wherein said natural amino acid comprises arginine-HCl.

9. The device of claim 6, wherein said synthetic amino acid comprises EDTA.

10. The device of claim 8, wherein said somatotropin, arginine-HCl and sucrose are in a weight:weight ratio of about 1:3:1 to about 1:1:3, respectively.

11. The device of claim 9, wherein said somatotropin, EDTA and sucrose are in a weight:weight ratio of about 2:1:30 to about 10:1:6.

12. The device of claim 6 containing sufficient Zn-pST to provide sustained release of bioactive Zn-pST for at least about 14 days.

13. The device of claim 1, wherein the matrix is contained within a bioltolerable container which comprises a length of silicon tubing or a wax casing.

14. The device of claim 13 further comprising a diffusion barrier which comprises at least one leucine or microporous polyethylene disk, said disk situated at one or both ends of said container.

15. The device of claim 5, wherein said Zn-pST matrix is in the form of one or more pellets.

16. The device of claim 15, wherein each of said pellets has a diameter of from about 3 to about 4 mm.

17. The device of claim 13, wherein said wax casing is selected from waxes including animal waxes, including beeswax, lanolin, shellac wax, or Chinese insect wax; vegetable waxes including hydrogenated soybean oil, hydrogenated cottonseed oil, carnauba, candelilla, bayberry, or sugar cane; mineral waxes including fossil or earth waxes including ozocerite, ceresin, or montan; or petroleum waxes including paraffin, microcrystalline, slack or scale wax; or combinations thereof.

18. An implantable device for the sustained release of bioactive Zn-porcine somatotropin comprising,

(a) a length of silicon tubing having at least one glass bead inserted at one end, wherein the inner diameter of said tubing and the diameter of said glass bead are substantially equal, such that the glass bead substantially seals the end of the tubing,

(b) a Zn-pST matrix comprising a mixture of Zn-pST, an amino acid capable of chelating Zn and

sucrose in a weight:weight ratio of from about 1:3:1 to about 1:1:3, respectively, said matrix formed into one or more pellets, wherein said pellet or pellets are inserted into said tubing adjacent said glass bead, and

(c) a diffusion barrier inserted at the end of said tubing opposite the end containing said glass bead, said diffusion barrier comprising a leucine disk.

19. The device of claim 18 wherein said amino acid comprises arginine-HCl.

20. The device of claim 18 wherein said amino acid comprises EDTA and said weight:weight ratio comprises about 8:1:16.

21. A process for improving the release characteristics of Zn-pST from an implantable sustained release device comprising admixing said Zn-pST with an amino acid capable of solubilizing Zn-pST at physiological pH and then loading said mixture into said sustained release device.

22. The process of claim 21, wherein said Zn-pST comprises recombinant pST.

23. The process of claim 21, wherein said amino acid comprises arginine-HCl.

24. The process of claim 21 wherein said amino acid comprises EDTA.

25. A method for delivering the sustained release of bioactive Zn-porcine somatotropin in a target animal comprising implanting in said target animal a biotolerable sustained release device which includes a matrix comprising a mixture of Zn-porcine somatotropin and an amino acid which solubilizes said Zn-porcine somatotropin at physiological pH, said device providing limited permeability to said matrix.

26. The method of claim 25, wherein said amino acid comprises arginine-HCl or EDTA, and said device

comprises a length of silicon tubing sealed at one end and comprising a diffusion barrier at the other end.

27. A method for providing the sustained release of bioactive Zn-porcine somatotropin in a target animal comprising implanting in said animal the implantable device of claim 18.

28. A method for providing the sustained release of growth promoting amount of Zn-porcine somatotropin to a target animal comprising implanting in said animal the implantable device of claim 22.

29. A method for providing the sustained release of growth promoting amount of Zn-porcine somatotropin to a target animal comprising implanting in said animal the implantable device of claim 23.

30. A method for delivering Zn-porcine somatotropin to a target animal in a sustained manner comprising implanting in said animal an implantable sustained release device which comprises a matrix of a mixture of Zn-pST, arginine-HCl and sucrose in a weight to weight ratio of about 1:3:1 to about 1:1:3 respectively, or a matrix of Zn-pST, EDTA and sucrose in a weight:weight ratio of about 8:1:16 within a container which is substantially impermeable to the exit of said matrix from said container, said container further comprising a diffusion barrier.

31. The process of claim 30, wherein said container comprises wax and said diffusion barrier comprises a leucine disc.

32. The method of claim 30, wherein said container comprises a length of silicon tubing having at least one glass bead substantially sealing one end of said tubing and having a diffusion barrier at the other end of said tubing.

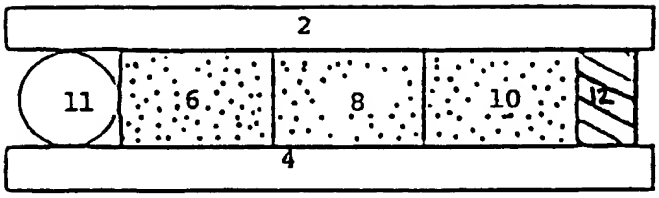


Figure 1

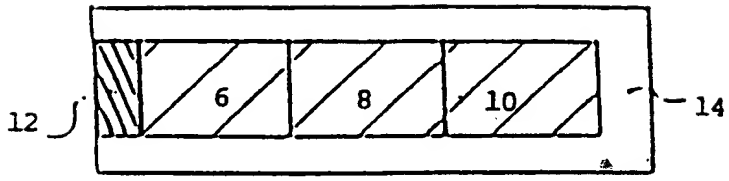


Figure 2

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K37/02; A61K9/20

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | A61K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | WO,A,9 011 070 (PITMAN-MOORE INC) 4 October 1990 | 1-7,10 |
| Y | see page 1, line 3 - line 6<br>see page 8, line 18 - page 9, line 10<br>see page 17; example 7<br>see claims 1,4,5 | 8,12-17, 19,21,22 |
| Y | EP,A,0 353 045 (AMERICAN CYANAMID COMPANY & RUTGERS, THE STATE UNIVERSITY OF NEW JERS.) 31 January 1990<br>see page 14 - page 15; example 5<br>see claims 1,3 | 12 |
| Y | US,A,4 765 980 (DEPRINCE R. ET AL) 23 August 1988<br>see column 6; example 2 | 13-16, 19,21 |

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 12 MAY 1993 | 10. 06. 93 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUR PEAN PATENT OFFICE | BOULOIS D. |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| Y | WO,A,9 105 548 (PITMAN-MOORE INC)<br>2 May 1991<br>see page 14, line 25 - page 15, line 24<br>see page 21; example 7<br>see claim 1 | 17,22 |
| Y | US,A,4 917 685 (VISWANATHAN R. ET AL)<br>17 April 1990<br>see column 7; example 1; table 1 | 8 |
| A | US,A,5 008 112 (VISWANATHAN)<br>16 April 1991<br>see column 11; example 1 | 1 |

# INTERNATIONAL SEARCH REPORT

PCT/US 93/00274

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 f first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 25-32 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9300274
SA 69650

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 12/05/93

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO-A-9011070 | 04-10-90 | AU-B- 634529 | 25-02-93 |
| | | AU-A- 5279290 | 22-10-90 |
| | | EP-A- 0463061 | 02-01-92 |
| | | JP-T- 4504122 | 23-07-92 |
| EP-A-0353045 | 31-01-90 | None | |
| US-A-4765980 | 23-08-88 | None | |
| WO-A-9105548 | 02-05-91 | AU-A- 6430190 | 16-05-91 |
| US-A-4917685 | 17-04-90 | None | |
| US-A-5008112 | 16-04-91 | None | |

FORMULATION FTO

## Record 1

asic Patent (No,Kind,Date): WO 9313792 A1 930722 PITMAN MOORE ← "Patent Family" report
)ELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES (English)
pplic (No,Kind,Date): WO 93US274 A 930108

------- Database Copyright --------- 04-16-1999 / 16:03:24 EST -----

'orld Patents - Legal Status data comes from the INPADOC database
nich is prepared 1999 by INPACDOC Patent Organization, Vienna,
ustria and made available by The Dialog Corporation plc.

## R cord 1

274891
asic Patent (No,Kind,Date): WO 9313792 A1 930722 <No. of Patents: 004>
atent Family:

| Patent No | Kind | Date | Applic No | Kind | Date | |
|---|---|---|---|---|---|---|
| AU 9335828 | A1 | 930803 | AU 9335828 | A | 930108 | application |
| CN 1074825 | A | 930804 | CN 93100374 | A | 930112 | application |
| MX 9300139 | A1 | 940729 | MX 9300139 | A | 930112 | application |
| WO 9313792 | A1 | 930722 | WO 93US274 | A | 930108 (BASIC) | application |

ority Data (No,Kind,Date):
WO 93US274 A 930108
US 820176 A 920113

TENT FAMILY:
STRALIA (AU)
atent (No,Kind,Date): AU 9335828 A1 930803 comp. spec., open to public
)ELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES (English)
Patent Assignee: PITMAN MOORE INC
Author (Inventor): RAMAN SIVA N; PRINCE RANDOLPH B DE; BLUM ALEKSANDER
Priority (No,Kind,Date): WO 93US274 A 930108; US 820176 A 920113
Applic (No,Kind,Date): AU 9335828 A 930108
PC: * A61K-037/02; A61K-009/20
CA Abstract No: * 119(14)146610W
Derwent WPI Acc No: * C 93-242909
Language of Document: English

INA (CN)
atent (No,Kind,Date): CN 1074825 A 930804 unexamined app., open to public
)ELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES (English)
Patent Assignee: PITMAN MOORE INC (US)
Author (Inventor): RAMAN SIVA N (US); PRINCE RANDOLPH B DE (US);
BLUM ALEKSANDER (US)
Priority (No,Kind,Date): US 820176 A 920113
Applic (No,Kind,Date): CN 93100374 A 930112
PC: * A61K-009/22; A61K-009/36; A61K-037/36
CA Abstract No: * 119(14)146610W
erwent WPI Acc No: * C 93-242909
anguage of Document: Chinese

XICO (MX)
tent (No,Kind,Date): MX 9300139 A1 940729 published application
ISPOSITIVO DE LIBERACION SOSTENIDA IMPLANTABLE. (Spanish)
atent Assignee: PITMAN MOORE INC (US)
uthor (Inventor): RAMAN SIVA N (US); PRINCE RANDOLPH B DE ( ); BLUM
ALEKSANDER
iority (No,Kind,Date): US 820176 A 920113
plic (No,Kind,Date): MX 9300139 A 930112
C: * A61D-007/00
A Abstract No: * 119(14)146610W
erwent WPI Acc No: * C 93-242909
anguage of Document: Spanish

)/ORLD INTELLECTUAL PROPERTY ORGANIZATION, PCT (WO)
Patent (No,Kind,Date): WO 9313792 A1 930722 publ. of int'l. app.
) DELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES (English)
Patent Assignee: PITMAN MOORE INC (US)
Author (Inventor): RAMAN SIVA N (US); DE PRINCE RANDOLPH B (US);
BLUM ALEKSANDER (US)
Priority (No,Kind,Date): US 820176 A 920113
Applic (No,Kind,Date): WO 93US274 A 930108
Designated States: (National) AU; BB; BG; BR; CA; FI; HU; JP; KP; KR;
LK; MG; MN; MW; NO; NZ; PL; RO; RU; SD; UA (Regional) AT; BE; CH;
DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG;
CI; CM; GA; GN; ML; MR; SN; TD; TG
Filing Details: WO 130000 With international search report; Before
expiration of time limit for amending the claims and to be
republished in the event of the receipt of the amendments
IPC: * A61K-037/02; A61K-009/20
CA Abstract No: ; 119(14)146610W
Derwent WPI Acc No: ; C 93-242909
Language of Document: English

)RLD INTELLECTUAL PROPERTY ORGANIZATION, PCT (WO)
egal Status (No,Type,Date,Code,Text):
/O 9313792 P 920113 WO AA PRIORITY (PATENT)
US 820176 A 920113
/O 9313792 P 930108 WO AE APPLICATION DATA (APPL. DATA)
WO 93US274 A 930108
/O 9313792 P 930722 WO AK DESIGNATED STATES CITED IN A
PUBLISHED APPLICATION WITH SEARCH REPORT
(DESIGNATED STATES CITED IN A PUBLISHED APPL.
WITH SEARCH REPORT)
AU BB BG BR CA FI HU JP KP KR LK MG MN MW NO
NZ PL RO RU SD UA
/O 9313792 P 930722 WO AL DESIGNATED COUNTRIES FOR
REGIONAL PATENTS CITED IN A PUBLISHED
APPLICATION WITH SEARCH REPORT (DESIGNATED
COUNTRIES FOR REGIONAL PATENTS CITED IN A
PUBLISHED APPL. WITH SEARCH REPORT)
AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT
SE BF BJ CF CG CI CM GA GN ML MR SN TD TG
/O 9313792 P 930722 WO A1 PUBLICATION OF THE INTERNATIONAL
APPLICATION WITH THE INTERNATIONAL SEARCH
REPORT (PUB. OF THE INTERNATIONAL APPL. WITH
THE INTERNATIONAL SEARCH REPORT)
/O 9313792 P 931111 WO DFPE REQUEST FOR PRELIMINARY
EXAMINATION FILED PRIOR TO EXPIRATION OF 19TH
MONTH FROM PRIORITY DATE
/O 9313792 P 950712 WO 122 EP: PCT APP. NOT ENT. EUROP.
PHASE (EP: PCT ANM. NICHT IN EUROP. PHASE
EING.)
/O 9313792 P 950913 WO NENP NON-ENTRY INTO THE NATIONAL
PHASE IN:
CA

FORMULATION F10

☒ **R c rd 1** ← "Patent Family" report

Basic Patent (No,Kind,Date): WO 9313792 A1 930722 PITMAN MOORE
DELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES (English)
Applic (No,Kind,Date): WO 93US274 A 930108



☐ **Record 1**

11274891
Basic Patent (No,Kind,Date): WO 9313792 A1 930722 <No. of Patents: 004>
Patent Family:

| Patent No | Kind | Date | Applic No | Kind | Date | |
|---|---|---|---|---|---|---|
| AU 9335828 | A1 | 930803 | AU 9335828 | A | 930108 | application |
| CN 1074825 | A | 930804 | CN 93100374 | A | 930112 | application |
| MX 9300139 | A1 | 940729 | MX 9300139 | A | 930112 | application |
| WO 9313792 | A1 | 930722 | WO 93US274 | A | 930108 (BASIC) | application |

Priority Data (No,Kind,Date):
WO 93US274 A 930108
US 820176 A 920113

PATENT FAMILY:
AUSTRALIA (AU)
Patent (No,Kind,Date): AU 9335828 A1 930803 comp. spec., open to public
DELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES (English)
Patent Assignee: PITMAN MOORE INC
Author (Inventor): RAMAN SIVA N; PRINCE RANDOLPH B DE; BLUM ALEKSANDER
Priority (No,Kind,Date): WO 93US274 A 930108; US 820176 A 920113
Applic (No,Kind,Date): AU 9335828 A 930108
IPC: * A61K-037/02; A61K-009/20
CA Abstract No: * 119(14)146610W
Derwent WPI Acc No: * C 93-242909
Language of Document: English

CHINA (CN)
Patent (No,Kind,Date): CN 1074825 A 930804 unexamined app., open to public
DELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES (English)
Patent Assignee: PITMAN MOORE INC (US)
Author (Inventor): RAMAN SIVA N (US); PRINCE RANDOLPH B DE (US); BLUM ALEKSANDER (US)
Priority (No,Kind,Date): US 820176 A 920113
Applic (No,Kind,Date): CN 93100374 A 930112
IPC: * A61K-009/22; A61K-009/36; A61K-037/36
CA Abstract No: * 119(14)146610W
Derwent WPI Acc No: * C 93-242909
Language of Document: Chinese

MEXICO (MX)
Patent (No,Kind,Date): MX 9300139 A1 940729 published application
DISPOSITIVO DE LIBERACION SOSTENIDA IMPLANTABLE. (Spanish)
Patent Assignee: PITMAN MOORE INC (US)
Author (Inventor): RAMAN SIVA N (US); PRINCE RANDOLPH B DE ( ); BLUM ALEKSANDER
Priority (No,Kind,Date): US 820176 A 920113
Applic (No,Kind,Date): MX 9300139 A 930112
IPC: * A61D-007/00
CA Abstract No: * 119(14)146610W
Derwent WPI Acc No: * C 93-242909
Language of Document: Spanish

WORLD INTELLECTUAL PROPERTY ORGANIZATION, PCT (WO)
Patent (No,Kind,Date): WO 9313792 A1 930722 publ. of int'l. app.
DELAYED RELEASE DEVICE FOR TRANSITION METAL/PROTEIN COMPLEXES (English)
Patent Assignee: PITMAN MOORE INC (US)
Author (Inventor): RAMAN SIVA N (US); DE PRINCE RANDOLPH B (US); BLUM ALEKSANDER (US)
Priority (No,Kind,Date): US 820176 A 920113
Applic (No,Kind,Date): WO 93US274 A 930108
Designated States: (National) AU; BB; BG; BR; CA; FI; HU; JP; KP; KR; LK; MG; MN; MW; NO; NZ; PL; RO; RU; SD; UA (Regional) AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; SN; TD; TG
Filing Details: WO 130000 With international search report; Before expiration of time limit for amending the claims and to be republished in the event of the receipt of the amendments
IPC: * A61K-037/02; A61K-009/20
CA Abstract No: ; 119(14)146610W
Derwent WPI Acc No: ; C 93-242909
Language of Document: English

WORLD INTELLECTUAL PROPERTY ORGANIZATION, PCT (WO)
Legal Status (No.Type,Date.Code,Text):

| | | |
|---|---|---|
| WO 9313792 | P 920113 | WO AA PRIORITY (PATENT) US 820176 A 920113 |
| WO 9313792 | P 930108 | WO AE APPLICATION DATA (APPL. DATA) WO 93US274 A 930108 |
| WO 9313792 | P 930722 | WO AK DESIGNATED STATES CITED IN A PUBLISHED APPLICATION WITH SEARCH REPORT (DESIGNATED STATES CITED IN A PUBLISHED APPL. WITH SEARCH REPORT) AU BB BG BR CA FI HU JP KP KR LK MG MN MW NO NZ PL RO RU SD UA |
| WO 9313792 | P 930722 | WO AL DESIGNATED COUNTRIES FOR REGIONAL PATENTS CITED IN A PUBLISHED APPLICATION WITH SEARCH REPORT (DESIGNATED COUNTRIES FOR REGIONAL PATENTS CITED IN A PUBLISHED APPL. WITH SEARCH REPORT) AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR SN TD TG |
| WO 9313792 | P 930722 | WO A1 PUBLICATION OF THE INTERNATIONAL APPLICATION WITH THE INTERNATIONAL SEARCH REPORT (PUB. OF THE INTERNATIONAL APPL. WITH THE INTERNATIONAL SEARCH REPORT) |
| WO 9313792 | P 931111 | WO DFPE REQUEST FOR PRELIMINARY EXAMINATION FILED PRIOR TO EXPIRATION OF 19TH MONTH FROM PRIORITY DATE |
| WO 9313792 | P 950712 | WO 122 EP: PCT APP. NOT ENT. EUROP. PHASE (EP: PCT ANM. NICHT IN EUROP. PHASE EING.) |
| WO 9313792 | P 950913 | WO NENP NON-ENTRY INTO THE NATIONAL PHASE IN: CA |